

CLINICAL STUDY PROTOCOL

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY OF EFFICACY OF THE ADMINISTRATION OF COLLOIDAL SILICON DIOXIDE IN TABLET DOSAGE FORM (CARBOWHITE) IN PATIENTS WITH ACUTE DIARRHEA

Sponsor:

Limited Liability Company “OmniFarma Kiev”

Sponsor’s representative

responsible for CS: O.V.Kurchenko, Candidate of Medical Science

Sponsor’s Medical and

Scientific Adviser: V.A.Tereshin, Post-doctoral Degree in Medicine, Professor

Protocol ID: CRID CODE-7-180

Version No: 1

Date: 08.06.2015

1. ABBREVIATIONS

DS – diarrheal syndrome

DBP – diastolic blood pressure

IP – investigational product

CS – clinical study

UE – undesirable effects

AR – adverse reaction

AE – adverse effect

SBP – systolic blood pressure

SUE – serious undesirable effects

HR – heart rate

2. CLINICAL STUDY REVIEW

ACTIVE INGREDIENT	Colloidal silicon dioxide (Aerosil 300 Pharma)
TITLE	Randomized, double-blind, placebo-controlled, multi-center study of efficacy of the administration of colloidal silicon dioxide in tablet dosage form (Carbowhite) in patients with acute diarrhea
Study objective	To demonstrate the antidiarrheal efficacy of colloidal silicon dioxide in tablet dosage form (Carbowhite) in patients with acute diarrhea.
Duration of study participation	- duration of study participation – 7 days. - study points: days 0, 1, 2, 3, 4, 5, 6, 7 of study.
Total expected number of patients	Approx. 144 enrolled patients.
Expected number of sites	3-5 sites
STUDY THERAPY Dosage form and composition of investigational product (IP)	1 tablet contains colloidal silicon dioxide with active sorption surface area of minimum 300 sq.m per 1 gram of the substance – 210 mg
Method of administration	Orally
Primary inclusion criteria	<ul style="list-style-type: none"> - signed Informed Consent Form for patient's study participation; - male and female patients at the ages from 18 to 55 years; - acute diarrhea (more than three episodes of liquid stool a day) within 48 hours or less in patients with usually normal stool*; - body temperature of $\leq 38^{\circ}\text{C}$; - patient's ability to adequately cooperate in the process of study.
Primary exclusion criteria	<ul style="list-style-type: none"> - aged of <18 or >55 years; - blood or pus in stool; - body temperature of $>38^{\circ}\text{C}$; - episodes of acute diarrhea for the last 30 days; - administration of antidiarrheal products for the last 24 hours; - salmonellosis (<i>Salmonella</i> of any serotype different from <i>S. typhi</i> and <i>S. paratyphi</i>; ICD-10: A02.0), dysentery (<i>Shigella dysenteriae</i>, <i>Shigella flexneri</i>, <i>Shigella boydii</i>; ICD-10: A03.0-A03.3), colibacillosis (<i>Escherichia coli</i>; ICD-10: A04.0-A04.4) which require administration of antimicrobial products; - pregnancy, lactation; - concomitant decompensated diseases or acute conditions which, according to an investigator, may

	<p>affect study results;</p> <ul style="list-style-type: none"> - alcoholism and drug abuse; - participation in any other clinical study.
DOSAGE REGIMEN:	<p>Initial dose**: IP/placebo is prescribed on Day 0 at a dose of: 3 tablets as a single dose (210 mg x 3 = 630 mg) t.i.d. (630 mg x 3 = 1,890 mg);</p> <p>IP/placebo dose escalation**: The IP/placebo dose escalation may be made on Days 1, 2, 3 and 4 in case of insufficient antidiarrheal efficacy (see Criteria of insufficient antidiarrheal therapy efficacy).</p> <p>IP/placebo dose escalation procedure: The IP/placebo dose escalation shall be made in two stages:</p> <ul style="list-style-type: none"> • Stage 1: 3 tablets as a single dose (210 mg x 3 = 630 mg) q.i.d. (630 mg x 4 = 2,520 mg); <p>Stage 1 can start on Day 1 or Day 2.</p> <ul style="list-style-type: none"> • Stage 2: 4 as a single dose (210 mg x 4=840 mg) q.i.d. (840 mg x 4 = 3,360 mg). <p>Stage 2 shall be implemented after Stage 1 only. For example, if a physician-investigator escalated the dose on Day 1 (Stage 1), Stage 2 can be implemented on Days 2, 3 or 4. If Stage 1 was implemented on Day 2, Stage 2 can be implemented on Days 3 or 4. In case of sufficient antidiarrheal efficacy (reduction in stool frequency per day) after dose escalation at Stage 1, Stage 2 may not be implemented.</p> <p>Dose reduction to the initial dose**: After the IP/placebo dose escalation according to p. 11.2, it may be reduced to the initial dose (see p. 11.1) in case of change in stool frequency to 3-4 times a day. The physician-investigator shall make such a decision in each particular case.</p> <p>Criteria of insufficient antidiarrheal efficacy:</p> <ul style="list-style-type: none"> • No reduction in stool frequency (per day) from the initiation of treatment with IP/placebo. <p>The physician-investigator may discontinue treatment with IP/placebo in case of any treatment failure criteria:</p> <p>Criteria of treatment failure:</p>

	<ul style="list-style-type: none"> • Increase in stool frequency (per day) from the initiation of treatment with IP/placebo. • No reduction or increase in stool frequency within a day after the IP/placebo initial dose escalation to a maximum daily dose (Stage 2). <p>Criteria of the end of treatment:</p> <ul style="list-style-type: none"> • Reduction in stool frequency to 3 times a day or less. • Verification of bacteriologic diagnosis with subsequent initiation of antibacterial therapy. • In case of any side effects associated, according to the physician-investigator, with the administration of IP/placebo.
SCHEDULE OF ASSESSMENTS	<p>Efficacy: see Study Schedule in Section 25.1.</p> <p>Safety: see Study Schedule in Section 25.2.</p> <p>Tolerance: see Study Schedule in Section 25.3.</p>
FORBIDDEN CONCOMITANT THERAPY	<p>Sorbents:</p> <ul style="list-style-type: none"> • Silicon dioxide containing products; • Activated carbon containing products; • Dioctahedral smectite; • Methyl-silicic acid hydrogel; • Lignin hydrolised • Combined sorbents. <p>Probiotics:</p> <ul style="list-style-type: none"> • <i>L. Plantarum</i> or <i>L. Fermentum</i> containing products; • <i>Bifidobacterium Bifidum I</i> containing products; • Other monoprobiotics, polyprobiotics and combined probiotics. <p>Prokinetics:</p> <ul style="list-style-type: none"> • Domperidone, metoclopramide, sulpiride. <p>Antimicrobial medicinal products (antibiotics, synthetic chemotherapeutic medicinal products) in cases when it is allowed for acute diarrhea – for example, bacterial foodborne intoxication, unspecified (ICD-10 A05.9), in mild and moderate disease.</p>

**the diagnosis of the disease associated with diarrhea shall be formulated by the physician-investigator as required by the Statistics Department of the medical institution (for example, bacterial foodborne intoxication, unspecified (ICD-10 A05.9), in mild and moderate disease).

** in all cases, IP/placebo shall be administered between meals (in 2 hours after or before meals).

3. STUDY SCHEDULE

DAYS	Screening 0	0	1	2	3	4	5	6	7
Inclusion/exclusion criteria	X	X							
Informed Consent	X								
Randomization (IWRS)		X							
Demographic determinants (gender, age) of the patient		X							
Life history and medical history		X							
Prior medical therapy		X							
Physical examination		X					X		
Vital signs (HR, SBP, DBP)		X	X	X	X	X	X	X	X
Body temperature		X	X	X	X	X	X	X	X
Body weight		X	X	X	X	X	X	X	X
Body height		X							
Fecal mass sampling for bacterial examination (if necessary)		X							
Handing-over of IP		X	X	X	X	X			
Records of concomitant medical therapy		X	X	X	X	X	X	X	X
EFFICACY									
Check of records in the Patient's Stool Quantity and Characteristics Diary			X	X	X	X	X	X	X
TOLERANCE									
Recording of AR/AE			X	X	X	X	X	X	X
SAFETY									
Recording of AE/SUE			X	X	X	X	X	X	X
Hematology, biochemistry of serum		X					X*		
Clinical urine examination		X					X*		
Urine pregnancy test (for women of child-bearing age)**		X							

* - if the patient was excluded on Days 1, 2, 3 or 4, safety assessment procedures for Day 5 shall be performed.

** - postmenopausal (over 2-year menopause) or women after surgical sterilization shall not take the pregnancy test.

4. INTRODUCTION AND JUSTIFICATION OF STUDY

Diarrhea is a medical condition characterized by frequent stool, more than 3 times (and more than 5-7 times in newborns) within the last 24 hours, and/or loose stool. The fecal matter is liquid, its daily mass exceeds 200 g per day, and water content reaches 95%. Diarrheal diseases are one of the main causes of mortality in developing countries [5, 6]. The largest economies show relatively low rate of mortality due to diarrheal diseases, but nonetheless, they are significant cause of morbidity and represent a material item of expenditure of the budget of public health service [6-8]. Traveller's diarrhea should be particularly noted as it is a specific group of diarrheal diseases that is becoming more

relevant and associated with permanent increase in the number of travellers [15, 18-20]. In a wide range of travelers' diseases, diarrhea takes the leading role – in average, it occurs in 20-60% of tourists [12]. The relevance of acute diarrhea is also associated with the necessity to solve a number of key issues arising during treatment, namely with patients' preference of self-arresting this medical condition [7, 13, 16].

In spite of the disease pattern, it is usually difficult to find out the cause of diarrhea in each particular case only based on symptoms and signs. There are acute (with the duration not exceeding 2-3 weeks) and chronic (with the duration of more than 3 weeks) diarrhea. There is also a notion of diarrheal syndrome (DS), i.e. diarrhea-induced symptomatology. DS means not only the diarrhea as itself but also abdominal pain, dehydration, fluid-and-electrolyte imbalance, intoxication and asthenia. Control of each such symptoms needs individual self-medication [7, 9, 13].

Causal treatment is optimal for any disease. To define etiology of diarrhea, plenty of time is required and a physician usually does not have it.

In view of this, treatment of any type of diarrhea includes two basic stages:

- symptomatic therapy to arrest the main signs of DS (frequent and bulky stool, pain syndrome, dehydration, intoxication);
- selection of causal treatment (it is possible only after laboratory verification of the pathogens of disease).

At conduction of symptomatic therapy of diarrhea, the administration of medicinal products not absorbed in the intestinal tract, i.e. locally acting (in the intestine lumen), is preferable [18]. Systemic effect on organism is excluded in this case. Quick antidiarrheal action of the product, as well as its high efficacy that allows its administration for a short period of time is critical issue [8].

Siliceous enterosorbent Carbowhite (IP) that has been developed on the basis of colloidal silicone dioxide (SiO_2) with active sorption surface area no less than 300 sq.m per 1 gram of a substance pertains these features to a large extent. It is suggested that silicone dioxide blocks the adhesion factors and causes denaturation of adhesive proteins on the bacterial cell surface, disturbing the functional activity and adhesive properties of the pathogenic microorganisms. Antimicrobial activity of silicon dioxide against enteric pathogens defines its antidiarrheal effect; three-dimensional structure of the sorbent increases viscosity of the liquid media, causing antidiarrheal and coating effect. Experiments on animals showed antidiarrheal effects of silicone dioxide (0.5-3% suspension) due to its ability to cause small bowel decontamination with a small bowel bacterial overgrowth syndrome; dose-dependent by 1.5-27 times, it reduced mediator-induced (cAMP, sodium desoxylate, serotonin) liquid accumulation in the intestinal tract of rats and stimulate *ex vivo* electrolyte and glucose absorption via the mucous membrane of small bowel of rats. During the oral administration of silicone dioxide (50-1,000 mg/kg), dose-dependent, it reduced frequency of defecation in case of non-infectious diarrhea in rats (castor oil; 0.5 ml/100 g, intragastrically); had therapeutic action in case of dyspepsia in calves; at a dose of 10 mg/kg, it reduced mortality due to diarrhea in piglets.

Single oral administration of silicone dioxide (300-1,000 mg/kg) does not affect the blood cell composition and causes minor transient changes in biochemical values. Long-

term administration of silicone dioxide at a therapeutic dose (150 mg/kg) does not affect the general state of pigs and metabolic values by increasing the body weight and reducing the quantity of triglycerides and cholesterol.

At its intake by animals, less than 1% of inorganic silicone is absorbed. After repeated 30-day intragastrical administration of silicone dioxide (100 and 1,500 mg/kg), no silicone accumulation is observed in organs and tissues of rats. Silicon dioxide in animal organisms is not subject to metabolic changes. After oral administration by rats and rabbits, more than 99% of silicone dioxide transits the intestinal tract and is excreted with fecal mass; small quantity of the absorbed silicone (less than 1%) is quickly excreted with urine. Silicon dioxide blocks the receptors of mucous membrane which are responsible for adhesion of microorganisms and toxin binding, thus, accelerating the absorption of medicinal products in the intestinal tract.

During assessment of its effect in human organism, it can be noted that silicone dioxide, like any other enterosorbents, has no systemic pharmacokinetics as its bioavailability makes less than 1%.

In various controlled clinical studies, in case of acute intestinal infection, infectious toxicosis syndrome, diarrhea and epigastric pain time reduction, quick remission, and inpatient stay term reduction were demonstrated with the administration of silicone dioxide for 3-5 days; at a dose of 0.5-0.75 g (*per os*, 4-6 times daily, 3-5 days), it promoted positive dynamics of disease pattern and complete eradication of the pathogen (according to bacteriological examination results), improved “average mass” molecule content in blood and immune complex level, inhibited abnormal activation of free-radical processes (according to biochemical examination results) against the background of diarrheal syndrome and epigastric pain time reduction by 2.1 days, post infectious asthenia signs time reduction by 4.8 days as compared to conventional therapy.

In the randomized controlled study of efficacy and safety of silicone dioxide (0.63-0.84 g, *per os*, 3-4 times daily, 15-20 days) in patients with drug-induced liver injury, high tolerability of the sorbent Carbowhite (tablets) and no undesirable reactions were observed.

That is why it is offered to conduct a randomized, double-blind, placebo-controlled, multi-center study of efficacy of the administration and safety of the sorbent Carbowhite (colloidal silicone dioxide) in patients with acute diarrhea.

4.1. Name and description of investigational product

Name: *Carbowhite*.

Composition:

active ingredient: colloidal silicone dioxide.

1 tablet contains 210 mg silicone dioxide;

excipients: microcrystalline cellulose, sorbite, potato starch, croscarmellose sodium, magnesium stearate.

Dosage form: tablets.

Method of administration: orally.

Pharmacologic class: sorbents. ATC code: A07B.

5. STUDY OBJECTIVE

To demonstrate the antidiarrheal efficacy of colloidal silicon dioxide in tablet dosage form (Carbowhite) in patients with acute diarrhea.

6. STUDY DESIGN

This clinical study is a randomized, double-blind, placebo-controlled, multi-center study where the colloidal silicon dioxide (Carbowhite) will be prescribed for the patients with acute diarrhea.

This study is conducted in compliance with requirements of the current legislation of Ukraine.

About 144 male and female subjects, age from 18 to 55 years old, for whom the enterosorbents were prescribed due to acute diarrhea will participate in the study.

Duration of study participation for each patient does not exceed 8 days.

7. PATIENT SELECTION

7.1. Patients' inclusion criteria:

- signed Informed Consent Form (Participant Information Sheet) for patient's clinical study;
- male and female subjects, age from 18 to 55 years old;
- acute diarrhea (more than 3 episodes of watery stool a day) during 48 hours or less in patients with normal stool usually*;
- body temperature $\leq 38^{\circ}\text{C}$;
- patient's ability to adequately cooperate during the study

*the diagnosis of the disease associated with diarrhea shall be formulated by the physician-investigator as required by the Statistics Department of the medical institution (for example, bacterial foodborne intoxication, unspecified (ICD-10 A05.9), in mild and moderate disease).

7.2. Patients' exclusion criteria:

- age <18 or >55 years old;
- the blood or pus in stool;
- body temperature $>38^{\circ}\text{C}$;
- the episodes of acute diarrhea for the last 30 days;
- the administration of anti-diarrheal medicinal products during 24 hours;
- salmonellosis (*Salmonella* of any serotype, different from *S. typhi* and *S. paratyphi*; ICD-10 code: A02.0), dysentery (*Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*; ICD-10 code: A03.0-A03.3), escherichiosis (*Escherichia coli*; ICD-10 code: A04.0-A04.4) requiring prescription of antibacterial medicines;
- pregnancy, lactation;
- concomitant decompensated diseases or acute conditions, in Investigator's opinion, are able to effect on the study results;
- alcoholism and drug abuse;
- participation in any other clinical study.

8. STUDY PROCEDURES BY VISITS

Section 2 describes the general study procedure schedule. The detailed list of procedures conducted at each visit is given below.

Day 0 (SCREENING AND RANDOMIZATION)

After a patient is admitted to Department of Infectious Disease, the physician-investigator shall estimate:

- the patient's possibility (provisional diagnosis, age) to participate in the study and shall offer him/her to participate;
- shall explain the essence of study participation to the patient.

Having received a preliminary consent for study participation, the patient shall be offered to familiarize himself/herself with the Patient Information. The physician-investigator must provide comprehensive answers to all questions the patient is interested in. After the consent is obtained, the patient shall sign an Informed Consent Form.

If at the moment of admission, it is not possible for the patient to familiarize himself/herself with a full version of the Patient Information in quiet atmosphere and get comprehensive answers to all questions in interest due to the patient's condition (frequent loose stool, asthenia, fever), he/she will sign the Patient Information Sheet (a brief version of the Patient Information). In this case, the physician-investigator shall provide an opportunity for the patient to familiarize himself/herself with the full version of the Patient Information and re-sign the Informed Consent Form within the first 24 hours of the study participation. If the patient refuses to sign the Informed Consent Form after his/her familiarization with the full version of the Patient Information, he/she will be excluded from the study as a consent withdrawn person.

The physician-investigator shall estimate all inclusion/exclusion criteria in whole (see subp. 7.1 and 7.2). The patient shall be interviewed (complaints, medical and life history) and his/her organs and systems shall be examined (general examination, skin and mucosae, respiratory, gastrointestinal, cardiovascular, and urogenital systems).

The following shall be recorded: patient's body weight, heart rate (HR), systolic and diastolic blood pressure (SBP and DBP). In case of compliance with inclusion criteria and no exclusion criteria, the patient shall be enrolled into the study.

The patient shall be randomized (via IWRS) in a study group. Thus,

- about 120 subjects will administer colloidal silicon dioxide (Carbowhite, IP);
- and about 24 subjects will administer placebo, i.e. at the ratio 5:1.

Prior to initiate treatment, the patient shall get a Patient's Stool Quantity and Characteristics Diary (see Annex 25.1). During Visit 1, the patient shall record data a day before admission. The physician-investigator must explain the correct filling in the diary to the patient.

The patient shall fill in the Patient's Stool Quantity and Characteristics Diary on a daily basis before the administration of a new daily dose of IP/placebo.

Before the patient receives any medical treatment, including IP/placebo, in the hospital department, he/she must have all necessary samples taken as provided by the Protocol (see Annex 25.2), as well as fecal matter taken for bacterial examination (if necessary).

The female subjects of child-bearing age must take urine pregnancy test.

Postmenopausal (over 2-year menopause) or women after surgical sterilization shall not take the pregnancy test.

After all laboratory tests have been made, the physician-investigator shall prescribe an initial dose of IP/placebo for the patient as per p. 11.1. All necessary medical treatment (rehydration and other symptomatic therapy) shall be also prescribed for the patient.

If the patient receives the medical treatment related to any other somatic diseases, these medicinal products must be administered not earlier than in 3 hours after the administration of IP/placebo.

The patient shall get the Patient's Stool Quantity and Characteristics Diary for Day 1 of treatment.

Day 1

The physician shall interview the patient (complaints) and examine him/her.

The following shall be recorded: patient's body temperature, HR, SBP and DBP.

The Patient's Stool Quantity and Characteristics Diary records shall be checked.

After the administration of the IP/placebo initial dose (see p. 11.1) within a day, the physician-investigator shall make a decision of the dosage regimen change, if necessary, as per p. 11.2. The decision of the dosage regimen change shall be taken by the investigator based on the assessment of the Patient's Stool Quantity and Characteristics Diary filled in by the patient after Day 1 of treatment.

UE/SUE recording.

The patient shall get the Patient's Stool Quantity and Characteristics Diary for Day 3 of treatment.

Day 2

The physician shall interview the patient (complaints) and examine him/her.

The following shall be recorded: patient's body temperature, HR, SBP and DBP.

The Patient's Stool Quantity and Characteristics Diary records shall be checked.

IP/placebo shall be further prescribed at the dosage regimen that was determined on Day 0 or 1 of study participation or escalated as per p. 11.2.

UE/SUE recording.

The patient shall get the Patient's Stool Quantity and Characteristics Diary for Day 3 of treatment.

Day 3

The physician shall interview the patient (complaints) and examine him/her.

The following shall be recorded: patient's body temperature, HR, SBP and DBP.

The Patient's Stool Quantity and Characteristics Diary records shall be checked.

In case of bacteriologic diagnosis verification, the physician shall make a decision whether a causal treatment is necessary. If it is necessary and the patient administers antimicrobial products, he/she shall discontinue study participation (see p. 12.2.). The patient's treatment with IP/placebo shall be discontinued.

The treatment can be also discontinued as required by other provisions of p. 12.2.

Laboratory examinations shall be made to estimate the IP/placebo treatment safety (see Annex 24.2.).

In case when the antimicrobial products are not prescribed, the patient shall continue study participation, IP/placebo shall be further prescribed in the following possible dosage regimen:

- till the end of the study the patient shall continue treatment in the dosage regimen that was determined on Day 0, 1 or 2 of treatment, or the physician-investigator shall make a decision of the dosage regimen change, if necessary, as per p. 11.2.
- the dose can be reduced to the initial dose (see p. 11.1.).

UE/SUE recording.

The patient shall get the Patient's Stool Quantity and Characteristics Diary for Day 4 of treatment.

Day 4

The physician shall interview the patient (complaints) and examine him/her.

The following shall be recorded: patient's body temperature, HR, SBP and DBP.

The Patient's Stool Quantity and Characteristics Diary records shall be checked.

The patient shall continue study participation, IP/placebo shall be further prescribed in the following possible dosage regimen:

- till the end of the study the patient shall continue treatment in the dosage regimen that was determined on Day 0, 1, 2 or 3 of treatment, or the physician-investigator shall take a decision of the dosage regimen change, if necessary, as per p. 11.2.
- the dose can be reduced to the initial dose (see p. 11.1.).

UE/SUE recording.

The patient shall get the Patient's Stool Quantity and Characteristics Diary for Day 5 of treatment.

Day 5

The physician shall interview the patient (complaints) and examine him/her.

The following shall be recorded: patient's body temperature, HR, SBP and DBP.

The Patient's Stool Quantity and Characteristics Diary records shall be checked.

The patient's treatment with IP/placebo shall be discontinued.

Laboratory examinations shall be made to assess the IP/placebo treatment safety (see Annex 25.2.).

UE/SUE recording.

The patient shall get the Patient's Stool Quantity and Characteristics Diary for Day 6 of treatment.

Day 6

The physician shall interview the patient (complaints) and examine him/her.

The following shall be recorded: patient's body temperature, HR, SBP and DBP.

The Patient's Stool Quantity and Characteristics Diary records shall be checked.

UE/SUE recording.

The patient shall get the Patient's Stool Quantity and Characteristics Diary for Day 7 of treatment.

Day 7

The physician shall interview the patient (complaints) and examine him/her.

The following shall be recorded: patient's body temperature, HR, SBP and DBP.
The Patient's Stool Quantity and Characteristics Diary records shall be checked.
Safety assessment according to laboratory parameters (hematology and biochemistry).
UE/SUE recording.
Study participation shall be discontinued.

9. CONCOMITANT THERAPY

Concomitant therapy is any therapy prescribed for the patient simultaneously with the administration of IP. The concomitant therapy should be minimal during the CS period. If the concomitant therapy is considered necessary for the patient and it is unlikely to interfere the IP therapy, it may be prescribed at the discretion of the investigator, with the stable dose preferable.

If the patient receives the medical treatment of other somatic diseases and administers symptomatic medicinal products (analgesics-antipyretics, etc.), these products should be administered no less than in 3 hours after the administration of IP/placebo.

Any concomitant therapy initiated before the CS and/or prescribed or changed during the CS should be indicated in the source documentation.

9.1. Forbidden concomitant therapy

The following products shall be forbidden during the clinical study participation due to their effect on stool frequency and characteristics:

Sorbents:

- Silicon dioxide containing products;
- Activated carbon containing products;
- Dioctahedral smectite;
- Methyl-silicic acid hydrogel;
- Lignin hydrolyzed;
- Combined sorbents.

Probiotics:

- *L. Plantarum* or *L. Fermentum* containing products;
- *Bifidobacterium Bifidum I* containing products;
- Other monoprobiotics, polyprobiotics and combined probiotics.

Prokinetics:

- Domperidone, metoclopramide, sulpiride.

Antimicrobial medicinal products (antibiotics, synthetic chemotherapeutic medicinal products)

in cases when it is allowed for acute diarrhea – for example, bacterial foodborne intoxication, unspecified (ICD-10 A05.9), in mild and moderate disease.

9.2 Permitted concomitant therapy

The investigator shall prescribe the medicinal products which are set out by standards of care of acute diarrhea (rehydration therapy), as well as symptomatic medicinal products (analgesics-antipyretics, etc.). The patient shall continue administering the medicinal products he/she administered due to concomitant somatic diseases.

10. INVESTIGATIONAL PRODUCT

10.1 Description of investigational product

The investigational product (IP) and placebo will be supplied by the Limited Liability Company “OmniFarma Kiev”.

The IP/placebo delivery frequency will depend on its availability, site potential for patients’ inclusion and IP shelf-life.

The investigational product (IP) and placebo are white biconvex tablets, 12 mm diameter.

10.2 Packaging

The IP and placebo are packed and labelled according to the Good Manufacturing Practice (GMP) and applied laws and provisions. The IP and placebo are packed to prevent their deterioration during transportation and storage.

All packages will be similar to observe double-blind study design. Each package will contain 80 tablets of the IP or placebo in total and will be intended for the administration by one patient for the whole treatment period.

10.3 Product accountability and storage

The Investigator shall record the IP/placebo dosage regimen administered by the patient in the source documentation (see below) on a daily basis. At the end of the last day of IP/placebo treatment (after the last administration), the physician-investigator shall count and record in the accounting form the total quantity of tablets administered during treatment period and the quantity of remaining IP/placebo tablets. The unused IP/placebo shall be kept in the site until returned to the Sponsor.

The Investigator shall be obliged to ensure proper storage of partially used and unused IP/placebo. Storage temperature requirements are from 0 to 25°C.

10.4 Product administration procedure (randomization procedure)

Centralized fixed block randomization is applied in the study.

To solve the given task, client-server architecture is used. The Sponsor of the study shall organize the central server (hereinafter – CS) operation both from hardware and software part. All the used software is provided with rightsholder’s licenses and approvals. Study Accounting Computer System (hereinafter – SACS) is server-based, and the sites shall have access to the SACS in the client mode, 24 hours a day. Hardware and software tools available at the site shall be used to ensure access. The Sponsor shall provide access to the SACS and technical support. In case of any technical malfunctions, the Sponsor shall resolve the problems arisen and restore the SACS normal operation.

The fixed block randomization is applied within the framework of the clinical study. The sites are the natural blocks. In terms of a block (a site), this method makes it possible, with a specified probability (at the ratio 5:1 in our case) to enroll a patient in a

real treatment or a placebo treatment group, with proportional ratio of these groups. The patient shall be enrolled in any of the groups on the basis of random numbers generated by the computer program.

Product (placebo or real) definition algorithm for a patient in the SACS:

1. Entering the source data in the SACS. At the stage of entering the patient's source data, the SACS monitors the patient's suitability for the study according to the parameters described in the Protocol. If the patient does not fit according to the key parameters, the SACS will not allow the patient's inclusion.

2. If the patient fits according to the key parameters, his/her data shall be entered in the SACS database, as well as the patient's anonymity and confidentiality shall be ensured. In this case, the SACS provides access to randomized product definition for the patient.

3. The randomized product definition for the patient consists of two stages:

3.1 a set of available products is defined in terms of the site. The set numbering begins with 0.

3.2 by means of random number generator with a range from 0 to the number of available products minus one, the SACS defines the index of the set of available products. The product with a defined index is assigned to the patient, and this product is excluded from the set of available products. The product is identified by the product batch labelling. The Sponsor shall provide labelling at the production stage considering that it should not be evident to define the kind of the product (placebo or IP).

Disclosure of randomization codes at the client level is not provided in the SACS.

10.5 Randomization code disclosure procedure

Randomization code disclosure takes place in case of serious AR/AE and when the physician considers that the future management of the patient can be determined only if the previous treatment (IP or placebo) of the patient is known.

Each product package with individual number will have the enclosed sealed envelope with information on tablet content (IP or placebo). The envelopes should be kept in at the site. The decision on envelope opening shall be taken by the physician-investigator who must inform the Sponsor on code disclosure within 24 hours. Upon study completion, the monitor checks the integrity of all envelopes whereof the appropriate report is drawn up.

The patient with the disclosed randomization code shall not be included into statistical processing of efficacy estimation but shall be included into treatment safety assessment.

10.6 Product return and disposal

The Sponsor shall be responsible for return and disposal of all the partially used or unused IP/placebo. The Returned IP/placebo Log will be given to the Investigator and then signed by the Investigator and monitoring group.

The Investigator shall not dispose the partially used or unused IP/placebo without the Sponsor's written authorization.

11. PRESCRIBED TREATMENT REGIMEN

The subjects will be randomized in 2 groups at the ratio 5:1:

1st group – about 120 subjects who will administer tablets containing colloidal silicon dioxide (Carbowhite - IP);

2nd group – about 24 subjects who will administer placebo.

In any case, the physician-investigator shall initiate treatment with an initial dose of IP/placebo that may remain unchanged till the end of the study or may change (see below).

11.1 Initial dose

On Day 0, IP/placebo is prescribed at the initial dose of: 3 tablets as a single dose (210 mg x 3 = 630 mg) t.i.d. (630 mg x 3 = 1,890 mg);

In all cases, IP/placebo is administered between meals (in 2 hours after or before meals).

11.2 Dose escalation to a maximum daily dose

IP/placebo dose escalation:

The IP/placebo dose escalation may be made on Days 1, 2, 3 and 4 in case of insufficient antidiarrheal efficacy (see Criteria of insufficient antidiarrheal therapy efficacy).

IP/placebo dose escalation procedure:

The IP/placebo dose escalation shall be made in two stages:

- Stage 1: 3 tablets as a single dose (210 mg x 3 = 630 mg) q.i.d. (630 mg x 4 = 2,520 mg);

Stage 1 can begin on Day 1 or Day 2.

- Stage 2: 4 as a single dose (210 mg x 4 = 840 mg) q.i.d. (840 mg x 4 = 3,360 mg).

Stage 2 shall be implemented after Stage 1 only.

For example, if the physician-investigator escalated the dose on Day 1 (Stage 1), Stage 2 can be implemented on Days 2, 3 or 4. If Stage 1 was implemented on Day 2, Stage 2 can be implemented on Days 3 or 4.

In case of sufficient antidiarrheal efficacy (reduction in stool frequency per day) after dose escalation at Stage 1, Stage 2 may not be implemented.

11.3 Dose reduction to the initial dose

After the IP/placebo dose escalation according to p. 11.2, it may be reduced to the initial dose (see p. 11.1) in case of change in stool frequency to 3-4 times a day.

The physician-investigator makes such a decision individually in each particular case.

12. END OF TREATMENT WITH INVESTIGATIONAL PRODUCT/PLACEBO

The physician-investigator may discontinue treatment with IP/placebo in case of the following criteria:

12.1 Insufficient antidiarrheal efficacy and treatment failure criteria

- No reduction of stool frequency (per day) from the initiation of treatment with IP/placebo.

The physician-investigator may discontinue treatment with IP/placebo in case of any treatment failure criteria (premature treatment discontinuation):

Treatment failure criteria:

- Increase of stool frequency (per day) from the initiation of treatment with IP/placebo.
- No reduction or increase of stool frequency within a day after the IP/placebo initial dose escalation to a maximum daily dose (Stage 2).

12.2 Treatment end criteria

- Reduction of stool frequency to 3 and less times a day, no loose stool.
- Bacteriological diagnosis verification with the consequent antibacterial therapy beginning.
- Development of adverse reactions associated, in the opinion of the physician-investigator, with the administration of IP/placebo.

12.3 CS participation premature discontinuation criteria

- The patient withdraws his/her signature under the Informed Consent Form.
- The patient refuses to sign the Informed Consent Form after familiarization with a full version of the Patient Information (when the patient familiarized with the Patient Information Sheet during screening and signed the Informed Consent Form).
- The patient refuses to be examined and follow the physician's instructions.
- The patient has the SUE associated, in the opinion of the physician-investigator, with the administration of IP.

13. DEFINITION OF SOURCE DOCUMENTATION

Data entered into the Case Report Forms (CRF) should be confirmed in the indentified and signed source documentation including, but not limited to, the following:

- Patient Information and Informed Consent Form;
- Patient Information Sheet and Informed Consent Form;
- Patient Identification Information (copies of outpatient medical records, case records, expert opinions, laboratory reports, etc.), last clinical study participation, medical history, concurrent diseases, and investigated disorder data;
- Previous and concomitant treatment;
- Date of the investigational product administration and dosage regimen;
- Date and time of visits and assessments, including the examination report;
- Vital signs (HR, SBP, DBP), body temperature, height, and weight;
- Laboratory reports;
- Undesirable effects (AR/AE) and follow-up control (in case of SUE, copies of epicrisis and examination reports evidencing the follow-up control must be included into the documentation);
- Date and reason for premature discontinuation (if any).

The source documentation may be as follows:

- Medical record;
- Photocopies of Patient Identification Information;
- Physician's documentation;
- Patient's Diary.

The Investigator must keep all the study documentation confidential for at least fifteen years and take measures to prevent its early destruction. If the Investigator's conditions do not guarantee the source documentation archiving, he/she must inform the Sponsor hereof and the documentation must be handed over to a third party (as mutually agreed). The Investigator shall enter the accurate data the CRF (according to the Sponsor developed technology) to register all observations and other CS related data (as instructed by the Sponsor).

The data computer processing by the Sponsor may result in additional requests (DCF) the Investigator must respond to. These requests and responses will add to CRF available by the Investigator and Sponsor.

14. STATISTICAL ASPECTS

14.1. DETERMINATION OF SAMPLE SIZE

At clinical study conduction, a minimum sample size that is sufficient to achieve study objectives is determined at the planning stage.

The minimum sample size shall be determined by a clinical effect value which presence (absence) is supposed to be found out and by a confidence level of the obtained conclusion which is defined with type I error probability (α – consumer's risk) and type II error probability (β – producer's risk).

Based on the placebo-controlled study objectives, one may come to a conclusion that to solve the formulated tasks it is necessary to estimate the percent of patients administered the investigational product who achieved the efficacy endpoint such as reduction in frequency of defecation to 3 times per day, absence of loose stool, on Day 5 or earlier (P_{product}). Based on preliminary studies, it is supposed that the expected probability of effect during the administration of the product will make $P_{\text{product}}=0.9$.

To estimate the minimum sample size that is sufficient for solving the formulated tasks, we used G*Power 3.1.5 (Heinrich-Heine-Universität Düsseldorf, 1992-2013) [3].

To verify statistical hypotheses, frequency comparison method for one group, Fisher exact test, two-sided critical range are used. When estimating the sample size, the standard levels of type I error probability $\alpha=0.05$ and type II error probability $\beta=0.2$ were chosen, 5% estimation error was chosen.

The protocol of calculations for this case is given in Table 1.

Thus, to solve the formulated task with the “consumer's risk” probability of $\alpha=0.05$ and “producer's risk” probability of $\beta=0.2$, 107 subjects will be sufficient.

Solving the safety assessment will require the calculation of percent of patients administered the investigational product who had undesirable effects. During the sample

size determination, the standard levels of type I error probability $\alpha=0.05$ and type II error probability $\beta=0.2$ were chosen, 5% estimation error was chosen. The calculations made for this case show that to solve this task with the “consumer’s risk” probability of $\alpha=0.05$ and “producer’s risk” probability of $\beta=0.2$, 32 subjects will be sufficient. Comparison of medicinal product efficacy vs placebo effect will require statistical hypotheses verification:

$$H_0: P_{\text{placebo}} = P_{\text{product}}$$

$$H_a: P_{\text{placebo}} \neq P_{\text{product}}$$

where P_{placebo} is a probability (incidence, %) of clinical effect achievement during the administration of placebo, and P_{product} is a probability (incidence, %) of clinical effect achievement during the administration of the investigational product.

To verify statistical hypotheses, incidence comparison method for two independent groups, Fisher exact test, two-sided critical range are used. When estimating the sample size, the standard levels of type I error probability $\alpha=0.05$ and type II error probability $\beta=0.2$ were chosen.

Considering the prognostic significance of diarrhea which may lead to significant liquid loss as well as the patient’s psychoemotional and physical discomfort, the placebo control group should be minimum allowed. Such approach will be ethically justified.

Thus, the assessment was conducted at the assumption of lesser quantity of subjects in placebo group, $N_{\text{product}}/N_{\text{placebo}}= 5$. According to the literature [1,2,4], the mean time for diarrheal syndrome arresting was 3 days during the administration of placebo, therefore, it can be accepted for this group that the expected probability of effect on Day 5 will make $P_{\text{placebo}}= 0.6$, and the expected probability of effect during the administration of the product will make $P_{\text{product}}= 0.9$. Hence, in the planned study it is suggested to find out the efficacy difference (if any) in 30%. The protocol of calculations for this case is given in Table 1.

Thus, to compare the investigational product efficacy vs placebo effect with the “consumer’s risk” probability of $\alpha=0.05$ and “producer’s risk” probability of $\beta=0.2$, 108 subjects will be sufficient (90 subjects in study group and 18 subjects in control group). Summarizing the obtained results (considering the probability of subjects’ discontinuation), we will find out that a minimum group of 144 subjects (120 subjects in study group and 24 subjects in control group) will be sufficient to:

- 1) estimate the percent of patients administered the investigational product who achieved the efficacy endpoint – reduction of defecation to 3 times a day, absence of loose stool, on Day 5 and earlier;
- 2) estimate the percent of patients administered the investigational product who had undesirable effects;
- 3) compare the medicinal product efficacy vs placebo effect, – with the level of type I error probability of $\alpha=0.05$ and type II error probability of $\beta=0.2$.

To obtain the representative sampling, it is planned to conduct study in 4 sites (30 subjects in study group and 6 subjects in control group for each site) and combine the obtained results using meta-analysis elements.

14.2 ANALYSIS ENDPOINTS

14.2.1. Demographic and initial characteristics

- Demographic determinants: gender, age
- Medical history;
- Prior medical therapy;
- Vital signs (HR, SBP, DBP);
- Body temperature;
- Physical examination (including body height and weight);
- Laboratory data.

14.2.2. Efficacy endpoints

Efficacy endpoint is the reduction in frequency of defecation to 3 or less times a day, absence of loose stool.

Primary efficacy parameters of investigational product

1. Percent of patients administered the investigational production who achieved the efficacy endpoint (reduction in frequency of defecation to 3 times per day, absence of loose stool) on Day 5 or earlier.

Secondary efficacy parameters of investigational product

1. Percent of patients administered the investigational production who discontinued the study.
2. Mean duration of treatment.
3. Mean quantity of tablets per treatment course.

14.2.3. Safety endpoints

Safety analysis shall be based on the following:

- Undesirable effects (adverse reaction / adverse effect – AR/AE);
- Vital signs (SBP, DBP, HR);
- Body weight;
- Laboratory test results: clinical and biochemical blood test, fluid-and-electrolyte balance, clinical urine test and urine pregnancy test.

Primary safety parameters of investigational product

1. Percent of patients administered the investigational production who had undesirable effects.

Secondary safety parameters of investigational product

1. Dynamics of vital sign change (SBP, DBP, HR).
2. Dynamics of body weight change
3. Laboratory test values: clinical and biochemical blood test, fluid-and-electrolyte balance, clinical urine test and urine pregnancy test.

14.3. STATISTICAL METHODS OF ANALYSIS

At primary and secondary variables analysis, the methods of descriptive statistics will be applied: at qualitative characteristics analysis the incidence rate (%) and standard error (m%) will be calculated; for quantitative characteristics in case of the normal statistical law the arithmetic mean value (\bar{X}) and standard deviation (SD) will be calculated; if statistical law differed from the normal one, the median value (Me), and the first and third quartile value (Q_I and Q_{III} , respectively) will be calculated. For assessment of the primary efficacy and safety parameters of the treatment, 95% confidence interval (95% CI) will be calculated. The Chi-squared test will be used at comparison of efficacy of medicinal product vs. placebo effect. During analysis the significance threshold has been chosen equal to 0.05.

To combine the results of 4 sites, meta-analysis elements will be used.

During parameters change dynamics analysis, ANOVA methods for the repeated measurements (or their non-parametric analogue) will be used.

The method of construction and analysis of the logistic regression models will be used for standardization of the potential risk factors for treatment failure.

In the course of analysis “Medstat” (Y.E.Lyach, V.G.Guryanov, 2004-2011) “MedCalc 15.6” (MedCalc Software, 1993-2015), G*Power 3.1.5 (Heinrich-Heine-Universität Düsseldorf, 1992-2013) statistical software will be used.

14.4 EFFICACY AND TOLERANCE/SAFETY STATISTICAL ANALYSIS PLAN

14.4.1 Initial homogeneity analysis

Initial homogeneity analysis is conducted by the age, gender, body weight and height, body mass index, physical examination factors, clinical and laboratory values.

To do this,

1) Use the methods of descriptive statistics to describe the baseline of each of two study groups (for quantitative variables in case of the normal statistical law: n, the arithmetic mean value (\bar{X}) and standard deviation (SD), minimum and maximum values; for quantitative variables if statistical law differs from the normal one: n, the median value (Me), and the first and third quartile value (Q_I and Q_{III} , respectively), minimum and maximum values; for categorical characteristics: n, incidence and percentage and standard error (m%).

2) For homogeneity estimation according to quantitative variables, compare the groups using the Student’s t-test for independent samples in case of normally distributed data or the Wilcoxon-W-test, if statistical law differs from the normal one, verify the two-sided hypothesis. Verify the normality of distribution using the D'Agostino-Pearson Test.

3) For homogeneity estimation according to categorical variables, compare the groups using the Chi-squared test with Yates correction (verify the two-sided hypothesis).

4) Make statistical conclusions on initial homogeneity of the compared groups according to the specified variables.

14.4.2 Tolerance/safety analysis

Tolerance/safety analysis will be performed for each of the variables according to the following scheme.

1) *Dichotomous variables describing presence of AR/AE/SUE.*

The values of descriptive statistics (incidence and percentage) will be defined for each study group for Days 1-5 of the study. Analyze the trend presence using the Chi-squared test.

2) *Quantitative variables describing the vital signs (HR, SBP, DBP, body temperature, body weight).*

In each study group, for each BP, Ps and thermometry parameter measured on Day 0 at the admission, and on Days 1-5, conduct one-way ANOVA test with repeated measurements (if statistical law differs from the normal one, use its non-parametric analogue, the Friedman test).

3) *Quantitative variables describing the biochemical blood test parameters, fluid-and-electrolyte balance values, clinical urine test.*

Define the values of descriptive statistics at study baseline and endpoint for each group. To find out the changes, compare the groups using the Student's t-test for linked samples in case of normally distributed data or the Wilcoxon-T-test, if statistical law differs from the normal one, verify the two-sided hypothesis.

14.4.3 Between-groups tolerance/safety comparison

1) *Dichotomous variables describing presence of AR/AE/SUE.*

The values of descriptive statistics (incidence and percentage) will be defined for each study group for 1-5 days of the study. Compare the percentage in each period for Days 1 and 5 using the Chi-square Test with Yates' correction and define if their difference is statistically significant.

2) *Quantitative variables describing the vital signs (HR, SBP, DBP, body temperature, body weight).*

In each study group, for each BP, Ps and thermometry parameter measured on Day 0 at the admission, and on Days 1-5. To find out the differences, compare two groups of patients in each period for Days 1 and 5. To compare, use the Student's t-test for independent samples in case of normally distributed data or the Wilcoxon-W-test, if statistical law differs from the normal one, verify the two-sided hypothesis.

3) *Quantitative variables describing the biochemical blood test parameters, fluid-and-electrolyte balance values, clinical urine test.*

Define the values of descriptive statistics at the study endpoint for each group. To find out the differences, compare the groups using the SUE's t-test for independent samples in case of normally distributed data or the Wilcoxon-T-test, if statistical law differs from the normal one, verify the two-sided hypothesis at the study endpoint.

4) Based on comparative analysis, make general conclusions on tolerance/safety.

14.4.4 Efficacy analysis

The product efficacy will be estimated for each group of variables according to the following scheme.

1) *Dichotomous variable* representing a percentage of patients administered the investigational product who achieved the efficacy endpoint – reduction in frequency of defecation to 3 times a day, absence of loose stool, on Day 5 and earlier.

Define the values of descriptive statistics (incidence and percentage) at the study endpoint for each group. The efficacy value is estimated in each group, its 95% CI is estimated.

2) *Quantitative variables: mean duration of treatment and mean quantity of tablets per treatment course.*

Define the values of descriptive statistics (Me, Q_I, Q_{III}, minimum and maximum values) at the study endpoint for each group.

14.4.5 Between-groups efficacy comparison

1) *Dichotomous variable* representing a percentage of patients administered the investigational product who achieved the efficacy endpoint – reduction in frequency of defecation to 3 times a day, absence of loose stool, on Day 5 and earlier.

The values of descriptive statistics (incidence and percentage) shall be defined at the study endpoint for each group. Compare the failure risks using the Chi-squared test with Yates correction and define if their difference is statistically significant. For quantitative estimation of the clinical effect, calculate the relative failure risk (RFR), Number-Needed-to-Treat, and estimate their 95% CI.

The method of construction and analysis of the logistic regression models shall be used for standardization of the potential risk factors for treatment failure. During the analysis, use the primary efficacy value as the output variable Y. For patients who achieved the efficacy endpoint – reduction in frequency of defecation to 3 times a day, absence of loose stool, on Day 5 and earlier, the value is Y=0, otherwise, Y=1. As the factorial features, conduct the analysis specified for gender, weight, height, body mass index, physical examination parameters, clinical and laboratory test values at baseline, as well as treatment procedure (IP/placebo). To select the treatment failure risk factors, use the inclusion/exclusion stepwise method (Stepwise, $p < 0.1$ for inclusion, $p > 0.3$ for exclusion). Based on model analysis, estimate the effect of the specified factorial features on the treatment failure risk (calculate the OR, 95% CI).

2) *Quantitative variables: mean duration of treatment and mean quantity of tablets per treatment course.*

Define the values of descriptive statistics at the study endpoint for each group. To find out the differences, compare the groups using the Wilcoxon-T-test at the study endpoint. Make the general conclusion on efficacy estimation, provide the efficacy value for the IP group (%), 95% CI), provide the efficacy value for the IP group vs. placebo group (RR, 95% CI, and NNT, 95% CI), provide the value of standardized (by other risk factors) failure risk for the IP group vs. placebo group (OR, 95%).

In all cases, during the analysis, select the significance threshold $\alpha_{\text{critical}} = 0.05$.

15. UNDESIRABLE EFFECTS MONITORING

All undesirable effects (AR/AE) will be recorded in the source documentation from the date of patients' signing the Informed Consent Form until the expiration of 2 days after

the administration of the last IP dose. They will be reported as set forth by the applied instructions and will be included into the CS final report.

15.1 UNDESIRABLE EFFECTS DEFINITIONS

15.1.1 Undesirable effects

Adverse reaction (AR) means all negative and unexpected responses to the introduction of medicinal product at any dose.

Adverse effect (AE) may be any undesirable and unexpected sign (including laboratory data change), symptom or disease which are concurrent with the administration of (investigational) medicinal product irrespective whether it is associated with the administration of (investigational) medicinal product or not.

15.1.2 Serious undesirable effect

Serious undesirable effect (SUE) is adverse clinical sign that, irrespective of a dose of the product, leads to:

- death;
- admission or admission prolongation;
- persistent or substantial disability and (or) incapacity;
- or is a congenial anomaly/ developmental disease.

15.2. INVESTIGATOR'S OBLIGATION AS TO THE UE (AR/AE) AND SUE REPORTING

15.2.1 General instruction for undesirable effects reporting

- All UE (AR/AE), starting from the date of signing the Informed Consent Form and until the CS completion, and irrespective of severity level and relation to the IP administration should be recorded on the relevant CRF pages.
- The Investigator, as soon as possible, shall inform of the diagnosis (or syndrome) stating from the first day, intensity, measures taken with regard to IP, prescribed therapy, additional examinations conducted, outcome, and his/her own opinion as to whether there is a reasonable possibility that the UE (AR/AE) was caused by the IP administration.

15.2.2 Instructions for serious undesirable effects reporting

In case of SUE, the physician-investigator shall immediately:

- Within the first working day, send the signed and dated CRF pages to the Sponsor's monitoring team representative by fax or e-mail (name, fax number, e-mail address is given in the CS Protocol).
- Enclose scan (photo) copies of all conducted examinations (with examination dates stated). The Investigator shall ensure the patient personal protection and properly specify the patient's ID in CS.
- All additional information should be sent to the Sponsor's monitoring team within the 1st working day from the date of its receipt.

15.3 SPONSOR'S OBLIGATION AS TO THE UE AND SUE REPORTING

In the course of CS, the Sponsor shall:

- Ensure compliance with regulatory requirements on UE (AR/AE) and SUE reporting set forth by the State Expert Centre of the Ministry of Health of Ukraine.
- Report, in an expedited manner, of all SUE unexpected or reasonably associated with the IP to the State Expert Centre of the Ministry of Health of Ukraine.

16. CONFIDENTIALITY

All the information provided by the Sponsor as well as received during the CS, namely CS Protocol, source documentation, CRF, Investigator's Brochure, and CS results shall be kept confidential till results publication. The Investigator and co-investigators shall respect confidentiality and do not disclose the CS information to the third party without the Sponsor's prior written consent.

This CS Protocol as well as other required documentation can be submitted to the Independent Ethics Committee, and the members of the Independent Ethics Committee must respect confidentiality.

The Sponsor and Investigator have agreed to respect confidentiality with regard to personal data of patients, investigator and employees involved in this CS.

17. PROPRIETARY RIGHTS

All information, documents and IP provided by the Sponsor shall be a Sponsor's sole property.

The Investigator may not refer to any information or IP in any patent applications or any other intellectual property rights applications.

The Sponsor may use or apply all the results at his own discretion without any limitations of his property rights. The Sponsor shall have no obligations on patenting, marketing or any other utilization of the CS results.

18. DATA PROTECTION

The patient's personal data to be entered into the Sponsor's database shall be protected in accordance with all applied laws and regulations.

The Sponsor shall take all necessary measures for patients' and investigator's (co-investigators') personal data protection to prevent access by the third parties.

19. INSURANCE INDEMNITY

The Sponsor shall prove the availability of the Certificate of Insurance covering the insured events related to the study participated.

If necessary, the Certificate of Insurance will be provided to the Ethics Committee.

20. SPONSOR AUDITS AND COMPETENT AUTHORITIES' INSPECTIONS

To adhere to the CS Protocol, Good Clinical Practice (GCP) and relevant regulatory requirements, the Investigator shall allow audits by the Sponsor and inspections by the relevant competent authorities.

The Investigator shall assist in audits/inspections providing access to all necessary documents and rooms which were used for CS anyway.

The Investigator shall agree that the auditors/inspectors get full access to the CS documentation for the purposes of analysis. The Investigator shall understand that these persons must keep professional secrecy and shall not disclose any CS related information.

The Investigator shall take all measures to solve the problems that were revealed during the audit/inspection.

21. CLINICAL STUDY RESULTS

The Sponsor shall be responsible for CS report preparation as well as for CS summary provision to the Investigator.

22. PUBLICATIONS AND REPORTS

The Investigator shall undertake not to disclose the CS and its results without the Sponsor's prior written approval. The Sponsor shall undertake not to limit publications without apparent causes.

Considering that this CS is conducted in several sites, the first publication will be made in the form of publication in all the sites involved in this Protocol fulfillment.

During the publication (report) preparation, the Investigator shall provide a script (presentation) for analysis at least 30 days before the publication submission (public speech).

The Investigator shall not use the Sponsor name in the publications (reports) without the Sponsor's prior written consent.

The Sponsor shall not use the Investigator (co-investigators) name(s) in advertising materials or publications without his/her (their) prior written consent.

Any publication (presentation) can be delayed for no more than 90 days in order the Sponsor could submit patent application or take other measures to prove his property rights.

The Sponsor shall have the right to publish the study results at any time.

23. ANNEXES AND AMENDMENTS TO CLINICAL STUDY PROTOCOL

All annexes to this Protocol referred to in the body of the Protocol shall be integral parts of the CS Protocol.

The Investigator cannot make amendments to the CS Protocol or allow for any departure from it without prior review and approval (or favorable opinion) by the Ethics Committee of the health care institution where the CS is conducted, except for the cases when it needs to be immediately done to avoid the risk to patient. Any agreed changes will be recorded in a written form. The written change will be signed by the Investigator and Sponsor as well as enclosed to the CS Protocol.

Any amendment to the CS Protocol needs to have approval (or favorable opinion) of the National Ethics Committee prior to be implemented if there are no safety reasons requiring to omit it.

24. LITERATURE REFERENCES

1. S.S. Vialov. Use of foodborne intoxication enterosorption therapy at pre-hospital stage / S.S. Vialov // *Meditsynskii Sovet.* - 2012. - No 3. - PP. 38–41.
2. Efficacy of up-to-date enterosorbent “Carbowhite” in patients with opportunistic acute intestinal infections / V.M. Frolov, T.P. Harnyk, O.V. Kruhlova [et al.] // *Phytotherapy. Chasopys.* – 2011. - No 4. – PP. 17-22.
3. Efficacy of enterosorption in complex therapy of patients with acute intestinal infections / V.O. Terioshyn, N.I. Khomutianska, O.V. Kruhlova, I.V. Dekaliuk // *All-Ukrainian Research and Practice Conference “Feral Herd Infections”* (Uzhhorod, May 17-18, 2012). – P. 101.
4. S.O. Kramarev Enterosorption for acute intestinal infections in children / S.O. Kramarev, O.A. Dmitrieva // *Zdorovye Rebenka.* – 2011. – No 2 (29). – PP. 77-80.
5. Batz M.B. Long-term consequences of foodborne infections / M.B. Batz, E. Henke // *Infect Dis Clin North Am.* – 2013. – Vol. 27(3). – P. 599-616.
6. Bicer S. A retrospective analysis of acute gastroenteritis agents in children admitted to a university hospital pediatric emergency unit / S. Bicer, D. Col, G.C. Erdag // *Jundishapur J Microbiol.* – 2014. - Vol. 7 (4). – P. 9148.
7. Burgmann K. Acute diarrhea / K. Burgmann, A. Schoepfer // *Ther Umsch.* – 2014. - Vol. 71 (9). – P. 529-535.
8. Dickinson B. Infectious diarrhea: an overview / B. Dickinson, C.M. Surawicz // *Curr Gastroenterol Rep.* – 2014. – Vol. 16 (8). - P. 399.
9. Efficacy of diosmectite (Smecta) in the treatment of acute watery diarrhoea in adults: A multicentre, randomized, double-blind, placebo-controlled, parallel group study / F.Khediri, A.I. Mrad, M. Azzouz, H. Doughi // *Gastroenterology Research and Practice.* – 2011. - <http://dx.doi.org/10.1155/2011/783196>
10. 2. Evaluation of diosmectite in acute diarrhea in children / C. Milocco, A. Bolis, V. Rizzo, T.Suprani // *Pediatrica medicae chirurgica.* – 1999. – Vol. 21, Issue 3. – P. 129-133.
11. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences / F. Faul, E. Erdfelder, A. Lang / 2007. *Behavior Research Methods.* – 2007. - P. 175-191.
12. Hill D.R. Travelers' diarrhea / D.R. Hill, N.J. Beeching // *Curr Opin Infect Dis.* – 2010. – Vol. 23 (5). – P. 481-487.
13. Kocoshis S.A. Medical management of pediatric intestinal failure / S.A. Kocoshis // *Semin Pediatr Surg.* – 2010. – Vol. 19 (1). – P. 20-26.
14. Lloyd R. Travellers' diarrhoea: causes, prevention and treatment / R. Lloyd, C. Bennett C. // *Nurs Stand.* – 2012. - Vol. 26(40). – P. 51-56.
15. McGregor A.C. Geographic, symptomatic and laboratory predictors of parasitic and bacterial causes of diarrhoea in travellers / A.C. McGregor, C. Whitty // *Trans R Soc Trop Med Hyg.* – 2012. – Vol. 106 (9). – P. 549-553.

16. Nothdurft H.D. Common forms of infectious diarrhea after trips abroad--what is proven and what is actually done? / H.D. Nothdurft, T. Löscher // Dtsch Med Wochenschr. – 2001. - Vol. 126. - P. 38-43.
17. Pozio E. Foodborne and waterborne parasites / E. Pozio // Acta Microbiol Pol. – 2003. - Vol. 52. – P. 83-96.
18. Rifaximin treatment of pathogen-negative travelers'diarrhea / H.L. DuPont , R. Haake, D.N. Taylor et al. // J Travel Med. – 2007. - Vol. 14. – P. 16-19.
19. Zaidi D. An update on travelers' diarrhea / D. Zaidi, E. Wine // Curr. Opin. Gastroenterol. – 2015. – Vol. 31 (1). – P. 7-13.
20. Zboromyrska Y. Aetiology of traveller's diarrhoea: evaluation of a multiplex PCR tool to detect different enteropathogens / Zboromyrska Y., Hurtado J.C., Salvador P. // Clin Microbiol Infect. – 2014. - Vol. 20(10). – P. 753-759.

25. ANNEXES

25.1 Efficacy assessment is conducted according to the Stool Quantity and Characteristics questionnaire.

Patient's Stool Quantity and Characteristics Diary

Date of issue of the Diary _____

Patient ID _____

Please fill in the Patient's Stool Quantity and Characteristics Diary. You should record the information on stool quantity and characteristics in this Diary*, **

Annex 25.1

Patient's Stool Quantity and Characteristics Diary

Frequency of defecation (specify the number)	Morning (06.00 a.m. till 12.00 a.m.)	Daytime (12.00 a.m. till 06.00 p.m.)	Evening (06.00 p.m till 12.00 p.m.)	Night (12.00 p.m. till 06.00 a.m.)
Total number of defecation a day				
Stool characteristics (put "X")				
Formed				
Unformed				
Soft				
Loose				
Mucous				
Bloody				
Other characteristics (to be specified)				

* at the date of admission, you shall fill in the information on stool quantity and characteristics observed during a day before hospitalization;

** on Days (0, 1, 2, 3, 4, 5 and 6) you shall record the information on stool quantity and characteristics for the previous day in the Diary and submit it to your attending physician on Days 1, 2, 3, 4, 5, 6 and 7, respectively.

25.2 Safety assessment is conducted according to the patients' laboratory test values (clinical and biochemical blood examination, fluid-and-electrolyte balance values, clinical urine examination), AE/SUE recording.

Annex 25.2.

Patients' Laboratory Test Values by Visits

Visits	Visit 1 (Day 0)	Visit 6 (Day 7±1) (Visit 3 or 4 in case of the patient's premature exclusion)
Clinical Blood Examination		
Erythrocytes (RBCs) , x10 ¹² /L	*	*
Hemoglobin, g/L	*	*
Color index, units	*	*
Hematocrit	*	*
Leukocytes (WBC), x10 ⁹ /L	*	*
Stab cells, %	*	*
Segmentated cells, %	*	*
Lymphocytes, %	*	*
Monocytes, %	*	*
Eosinophils, %	*	*
Basophils, %	*	*
Platelets, x10 ⁹ /L	*	*
ESR, mm/h	*	*
Clinical Urine Examination		
Specific gravity, g/L	*	*
pH, units	*	*
Protein, g/L	*	*
Glucose, g/L	*	*
Leukocytes, number per field of view	*	*
Erythrocytes, number per field of view	*	*
Epithelial cells, number per field of view	*	*
Biochemical Blood Examination		
Total protein, g/L	*	*
ALT, µmol/L×h	*	*
AST, µmol/L×h	*	*
Bilirubin (total), µmol/L	*	*
Creatinine, µmol/L	*	*
Urea, mmol/L	*	*
Blood glucose, mmol/L	*	*
Fluid-and-Electrolyte balance Values		
Sodium, mmol/L	*	*
Potassium, mmol/L	*	*

25.3 Tolerance assessment is conducted according to AR recording.

**PATIENT INFORMATION AND INFORMED CONSENT FORM
(ACCORDING TO GCP 4.8 AND
PERSONAL DATA PROTECTION REQUIREMENTS)**

**Randomized, Double-Blind,
Placebo-Controlled, Multi-Center Study
of Efficacy and Safety of the Administration of Colloidal Silicon Dioxide
in Tablet Dosage Form (Carbowhite)
in Patients with Acute Diarrhea**

Version No: 1

Date: _____

Principal Investigator: _____

Patient ID: _____

Address and telephone number of Ethics Committee in:

INTRODUCTION

We kindly invite you to take part in the clinical study. According to the physician-investigator, you meet the study basic requirements. Prior to give your consent to study participation, it is important for you to read and understand the information given in this document. It describes the purpose, procedures, advantages, potential risks and inconveniences related to this study, as well as your obligations as a study participant. It also describes alternative procedures available for you and your rights for study participation discontinuation at any time. No warranties and statements are made with regard to the study results. After you familiarize yourself with this document and receive all answers to the questions you are interested in, you will be offered to sign the Consent Form.

You can do harm yourself if you fail to give true and realistic answers concerning your medical history, administration of prescription and non-prescription medicinal products before and at the present time to your physician-investigator.

STUDY OBJECTIVE

Diarrhea is a medical condition characterized by frequent stool, more than 3 times (and more than 5-7 times in newborns) within the last 24 hours, and/or loose stool. The fecal matter is liquid, its daily mass exceeds 200 g per day, and water content reaches 95%. Diarrheal diseases are one of the main causes of mortality in developing countries. The largest economies show relatively low rate of mortality due to diarrheal diseases, but nonetheless, they are significant cause of morbidity and represent a material item of expenditure of the budget of public health service.

In spite of the disease pattern, it is usually difficult to find out the cause of diarrhea in each particular case only based on symptoms and signs. There are acute (with the duration not exceeding 2-3 weeks) and chronic (with the duration of more than 3 weeks) diarrhea. There is also a notion of diarrheal syndrome (DS), i.e. diarrhea-induced symptomatology. DS means not only the diarrhea as itself but also abdominal pain, dehydration, fluid-and-electrolyte imbalance, intoxication and asthenia. Control of each such symptoms needs individual self-medication.

Causal treatment, i.e. the treatment addressing the causes of the disease, is optimal for any disease. To define etiology of diarrhea, plenty of time is required and a physician usually does not have it.

In view of this, treatment of any type of diarrhea includes two basic stages:

- symptomatic therapy to arrest the main signs of DS (frequent and bulky stool, pain syndrome, dehydration, intoxication);
- selection of causal treatment (it is possible only after laboratory verification of the pathogens of disease).

At conduction of symptomatic therapy of diarrhea, the administration of medicinal products not absorbed in the intestinal tract, i.e. locally acting (in the entodermal canal lumen), is preferable. Systemic effect on human body is excluded in this case. Quick antidiarrheal action of the product, as well as its high efficacy that allows its administration for a short period of time is critical issue.

Silica-based eneterosorbent developed on the basis of colloidal silicone dioxide (SiO_2) Carbowhite (IP) fits these properties to a great extent. The product has a large sorption surface (active sorption surface area) is no less than 300 sq.m per 1 gram of the substance) as well as high binding rate of bacteria and their toxins that provides for quick therapeutic (antidiarrheal) effect. In addition, the colloidal silicone dioxide pharmacological profile is associated with its good safety profile.

Silicone dioxide is produced in the form of powder for suspension that is not always easy to administer. The Carbowhite product is of tablet dosage form containing 210 mg of colloidal silicone dioxide. Tablets are more suitable for consumers.

This study objective is to estimate the antidiarrheal efficacy and safety of the administration of tablet dosage form of colloidal silicone dioxide (Carbowhite) in patients with acute diarrhea.

If you meet the inclusion criteria, the IP/placebo treatment will be prescribed for you. By its appearance, placebo does not differ from the colloidal silicon dioxide tablets, but it does not contain active ingredient.

The IP/placebo dose initially prescribed for you will be 3 tablets as a single dose (210 mg x 3 = 630 mg) t.i.d. (630 mg x 3 = 1,890 mg). This dose may be escalated to 3 tablets as a single dose (210 mg x 3 = 630 mg) q.i.d. (630 mg x 4 = 2,520 mg) on Day 1 or Day 2 if the product antidiarrheal efficacy is insufficient. On Day 3 and Day 4, the IP/placebo dose may be escalated to 4 as a single dose (210 mg x 4 = 840 mg) q.i.d. (840 mg x 4 = 3,360 mg) if the IP/placebo dose was escalated on Day 1 or Day 2.

In case of IP/placebo treatment failure (stool frequency increase) you can be excluded and another treatment will be prescribed for you.

After the bacteriological diagnosis verification (in 3 days, usually), if the physician-investigator considers it necessary to prescribe antimicrobial products, your IP/placebo treatment will be discontinued. If the antimicrobial products are not prescribed, the IP/placebo treatment can be prolonged up to 5 days.

In the course of treatment, other products provided by the standards of care of patients with bacterial foodborne intoxication will be prescribed for you. The physician-investigator shall define the prescription of these products.

STUDY DESCRIPTION

This study shall be conducted in several hospitals of infectious diseases of Ukraine.

About 140 adult patients with acute diarrhea will participate in the study. Your study participation will last about 7 days.

If you agree to participate in this study and meet all the participation requirements, you will be offered to do the following depending on the study period.

Day 0

Screening period

Screening period starts after the patient was admitted to the Department of Infectious Disease and the diagnosis of bacterial foodborne intoxication unspecified (moderate). Then the physician-investigator shall:

- estimate your possibility to participate in the study and offer you to participate;
- explain the essence of study participation to you.

Having received a preliminary consent for study participation, you will be offered to familiarize yourself with the Patient Information. The physician-investigator must provide comprehensive answers to all questions you are interested in. After the consent is obtained, you will be offered to sign the Informed Consent Form.

You will be asked about your birth date, gender, complaints, medical history, prior and concurrent diseases, medicinal products you administer due to other diseases. It is very important to give accurate and full information on these questions. Provision of untrue, incomplete or false information about your medical history, including information about medicinal products administered at the moment or before, can lead to negative consequences for your health.

You will take physical examination with the measurement of the body height and weight, as well as body temperature, blood pressure and pulse.

You will be explained how to fill in the Patient's Stool Quantity and Characteristics Diary and asked to fill it in. In this Diary, you will have to record the information on stool quantity and characteristics, gastrointestinal tract conditions a day before hospitalization.

Blood sampling will be made for the purposes of the following examinations:

- clinical examination – erythrocytes, hemoglobin, hematocrit, leucocytes, monocytes, erythrocyte sedimentation rate;
- biochemistry – total protein, aspartate aminotransferase, alanine aminotransferase, bilirubin, creatinine, urea, glucose;
- fluid-and-electrolyte balance values – sodium, potassium.

The blood is sampled from the vein, at least twice (before treatment and during the final visit), approx. by 10 mL. In total, up to 20 mL of blood will be sampled that corresponds to 4 tea spoons.

Urine sampling will be made for the purposes of the clinical examinations to define specific gravity, pH, protein, glucose, erythrocytes, leucocytes, epithelial cells and salts. Also, fecal masses will be sampled for bacteriological examination.

For women of child-bearing age, urine pregnancy test will be made as the pregnant women must not participate in this clinical study.

During the screening period that lasts for up to 3-4 hours you will not administer IP/placebo.

Randomization and treatment initiation

Upon the screening period completion, you will be randomized, i.e. by random sampling technique included into one of the groups:

Group 1 – patients administering colloidal silicon dioxide (Carbowhite, IP);

Group 2 – patients administering placebo.

By its appearance, placebo does not differ from the colloidal silicon dioxide tablets (Carbowhite) but it does not contain active ingredient. The assignment by groups at the ratio 5:1 will be done, i.e. about 120 patients will administer colloidal silicon dioxide (Carbowhite, IP), and 24 – placebo.

After randomization, an initial dose of IP/placebo will be prescribed for you:

IP/placebo is prescribed at a dose of: 3 tablets as a single dose ($210\text{ mg} \times 3 = 630\text{ mg}$) t.i.d. ($630\text{ mg} \times 3 = 1,890\text{ mg}$).

You will be given the Patient's Stool Quantity and Characteristics Diary to record necessary information during the next day. The Patient's Stool Quantity and Characteristics Diary is given on each next day of treatment (1, 2, 3, 4, 5 and 6).

Day 1

The physician-investigator will ask you about the complaints. Your body temperature, blood pressure and pulse will be measured. These procedures are taken at the beginning of each next day of treatment (2, 3, 4, 5, 6 and 7).

The physician-investigator will check your Patient's Stool Quantity and Characteristics Diary records. This is made at the beginning of each next day of treatment (2, 3, 4, 5, 6 and 7). Based on these data, the physician-investigator shall make a decision whether to remain the prescribed IP/placebo dose or escalate it: 3 tablets as a single dose (210 mg x 3 = 630 mg) q.i.d. (630 mg x 4 = 2,520 mg).

Day 2

The physician-investigator will check your Patient's Stool Quantity and Characteristics Diary records.

Based on the data you stated in the Patient's Diary, the physician-investigator shall make a decision whether to continue treatment with the dosage regimen that was determined on Day 0 or escalate it: 3 tablets as a single dose (210 mg x 3 = 630 mg) q.i.d. (630 mg x 4 = 2,520 mg).

The decision on your discontinuation shall be taken in case of insufficient antidiarrheal efficacy of the treatment conducted.

In case of IP/placebo treatment discontinuation, you will have your blood sampled for examinations (clinical and biochemical examinations, fluid-and-electrolyte balance values), as well as urine sampled for clinical examination.

In case of discontinuation, another treatment will be prescribed for you.

Day 3

Based on the fecal mass bacteriological examination results, the pathogen can be determined. The physician-investigator can make a decision on prescription of antimicrobial products for you. In this case, you will be excluded from the study.

The physician-investigator can make a decision on your IP/placebo treatment discontinuation if:

- diarrhea stopped (stool frequency does not exceed 3 times a day, formed stool);
- antidiarrheal efficacy of the conducted IP/placebo treatment is insufficient.

In case of exclusion from the study, you will have your blood and urine sampled for examinations as described in the procedures (Day 2).

Irrespective of the fecal mass bacteriological examination results, the physician-investigator may take a decision on your further study participation. In this case, treatment with IP/placebo shall continue with the dosage regimen determined by the physician-investigator:

- the dose that was determined on Day 1 or Day 2;
- the dose can be escalated to 4 tablets as a single dose (210 mg x 4 = 840 mg) q.i.d. (840 mg x 4 = 3,360 mg) if it was escalated on Day 1 or Day 2;
- the dose that was determined on Day 0 (initial dose).

Day 4

Your treatment with IP/placebo can be discontinued if the diarrhea stopped (stool frequency does not exceed 3 times a day, formed stool).

In case of IP/Placebo treatment discontinuation, you will have your blood and urine sampled for examinations as described in the procedures (Day 2).

In case of IP/Placebo treatment discontinuation on Day 2, the physician-investigator shall inform you about the blood and urine examination results.

If the treatment with IP/placebo continues, the dosage regimen shall be determined by the physician-investigator described in the procedures (Day 3).

Day 5

Treatment with IP/placebo stops.

You will have your blood sampled for examinations (clinical and biochemical examinations, fluid-and-electrolyte balance values), as well as urine sampled for clinical examination.

In case of IP/Placebo treatment discontinuation on Day 3, the physician-investigator shall inform you about the blood and urine examination results.

Day 6

The above procedures are taken. In case of IP/Placebo treatment discontinuation on Day 4, the physician-investigator shall inform you about the blood and urine examination results.

Day 7

The physical examination and above procedures are taken. The physician-investigator shall inform you about the blood and urine examination results obtained on Day 5.

Study participation is stopped.

POTENTIAL EXPECTED BENEFITS

Colloidal silicone dioxide (Carbowhite) may help you recover from diarrhea. In the course of this study, you can benefit from medical supervision that will be performed during visits. We hope the information obtained from this study will provide valuable data and help improve treatment of patients with diarrhea in case of bacterial foodborne intoxication.

POTENTIAL RISKS

Like any other medicinal product, colloidal silicone dioxide (Carbowhite) can cause adverse reactions. Nevertheless, this does not mean that you will have the adverse reactions for sure. The literature data demonstrate that usually the product is well-tolerated by patients. Potential long-term adverse effects and serious risks associated with the administration of colloidal silicone dioxide (Carbowhite) are not expected to occur.

You can experience some short-term and/or minor discomfort during blood sampling: pain caused by a needle entering the vein or dizziness. In case of the mentioned symptoms, report to medical staff who make such manipulation hereof.

ALTERNATIVE TREATMENT

This study participation is not a prerequisite for your treatment. There are other treatment methods available. If you decide not to participate in this study, please ask you

physician-investigator about alternative treatment. You and your physician-investigator can decide what treatment is better for you.

STUDY PARTICIPANT'S OBLIGATIONS

In the course of study participation, you must not administer any other antidiarrheal products. The physician-investigator will discuss with you which treatment is allowed before inclusion. If you administer any medicinal products due to concurrent diseases, changing the mode of their administration may be necessary. The physician-investigator will inform you hereof.

EXPENSES AND PAYMENT FOR STUDY PARTICIPATION

In the frameworks of the study, you will get the investigational product and take all tests and procedures free of charge.

Your study participation will not imply any extra material costs.

Payment to the patient for study participation is not provided.

INSURANCE

The Certificate of Insurance for this clinical study as required by the current legislation was received in the insurance company

“ _____ ”,

with legal address _____

Tel: _____.

Insurance Contract No _____.

This Certificate of Insurance shall cover the responsibility of possible harmful effect caused to life and health of the patients by the clinical study.

CONFIDENTIALITY

Only the physician-investigator, medical staff, Sponsor and his legal representatives, the Ministry of Health of Ukraine and its authorized bodies, governmental agencies of other countries where colloidal silicone dioxide (Carbowhite) is planned for approval and the local ethics committee shall have access to medical documentation and medical data obtained in the course of the clinical study.

Your personal data shall be kept by the physician-investigator and his/her medical staff and shall not be disclosed, including the study data publications.

The Sponsor and physician-investigator shall guarantee confidentiality of your personal medical data in accordance with the current legislation of Ukraine.

DISCONTINUATION OF STUDY PARTICIPATION

You may voluntarily discontinue your participation at any time. If you decided to refuse from study participation, you should inform the physician-investigator hereof. The physician-investigator shall discuss further treatment with you.

The physician-investigator can discontinue your participation due to many reasons even if you do not wish. These reasons may include such circumstances as unwillingness to undergo examination or follow the physician's instructions. In this case, the administration of the investigational product will be stopped. The physician-investigator shall discuss further treatment with you.

Even if you discontinued study participation, you may be asked to stay for further supervision for safety purposes.

INFORMED CONSENT FORM

Study title: randomized, double-blind, placebo-controlled, multi-center study of efficacy and safety of the administration of colloidal silicon dioxide in tablet dosage form (Carbowhite) in patients with acute diarrhea.

Sponsor: Limited Liability Company “OmniFarma Kiev”

Full name of the responsible investigator: _____

Address: _____

Patient ID: _____

By signing this document, I shall confirm that:

1. I have read this Patient Information and Informed Consent Form in an understandable language and got answers to all interested questions concerning this study.
2. I have had sufficient time to make a decision.
3. I voluntarily agree to participate in the study described in this Patient Information and Informed Consent Form.
4. I was informed of the names of study team members whom I can contact.
5. I agree that the Sponsor, medical staff of the study and other persons will have access to my medical history as described in this Patient Information and Informed Consent Form.
6. I have got the secondary original of this Patient Information and Informed Consent Form to be kept by me.

Patient's signature

Date (dd/mm/yyyy)

Full name of the patient (please print with your own hand)

Physician-investigator's signature

Date (dd/mm/yyyy)

Full name of the physician-investigator (please print with your own hand)

**PATIENT INFORMATION AND INFORMED CONSENT FORM
(ACCORDING TO GCP 4.8 AND
PERSONAL DATA PROTECTION REQUIREMENTS)**

**Randomized, Double-Blind,
Placebo-Controlled, Multi-Center Study
of Efficacy and Safety of the Administration of Colloidal Silicon Dioxide
in Tablet Dosage Form (Carbowhite)
in Patients with Acute Diarrhea**

Version No: 1

Date: _____

Principal Investigator: _____

Patient ID: _____

Address and telephone number of Ethics Committee in:

Due to your condition, it is not possible for you to familiarize yourself with a full version of the Patient Information, that's why you are offered to read brief information about the clinical study (CS) and participate in it. If you agree to participate in the CS, you should familiarize yourself with the full version of the Patient Information in the nearest time, but not later than in a day. According to the physician-investigator's opinion, you meet the initial requirements of this study.

Diarrhea is a medical condition characterized by increase in stool frequency more than 3 times for the last 24 hours and/or stool softening.

The medicinal products not absorbed in the intestinal tract are usually used in the course of diarrhea symptomatic therapy. Silica-based enterosorbent Carbowhite (IP) developed on the basis of colloidal silicone dioxide (SiO₂) fits these properties. The product has a large sorption surface as well as high binding rate of bacteria and their toxins that provides for quick therapeutic (antidiarrheal) effect.

The study objective is to estimate the antidiarrheal efficacy of the administration of colloidal silicon dioxide in tablet dosage form (Carbowhite) in patients with acute diarrhea.

During the screening period, the inclusion/exclusion criteria will be estimated to define the possibility of your participation in the CS. Upon screening period completion, you will be randomized, i.e. by random sampling technique included into one of the groups: Group 1 – patients administering tablets containing the IP; Group 2 - patients administering placebo. By its appearance, placebo does not differ from the colloidal silicon dioxide tablets (Carbowhite), but it does not contain active ingredient.

After randomization, an initial dose of IP/placebo will be prescribed for you at a dose of: 3 tablets as a single dose ($210\text{ mg} \times 3 = 630\text{ mg}$) t.i.d. ($630\text{ mg} \times 3 = 1,890\text{ mg}$). During the treatment the IP/placebo dose can vary at the physician-investigator's discretion or depending on your condition.

Treatment with IP/placebo will last for no more than 5 days. You may terminate CS participation at any of its stages. In this case, the physician shall discuss further treatment with you. Participation in this CS is not a prerequisite for your treatment.

INFORMED CONSENT FORM

Study title: randomized, double-blind, placebo-controlled, multi-center study of efficacy and safety of the administration of colloidal silicon dioxide in tablet dosage form (Carbowhite) in patients with acute diarrhea.

Sponsor: Limited Liability Company “OmniFarma Kiev”

Full name of the responsible investigator: _____

Address: _____

Patient ID: _____

By signing this document, I shall confirm that:

1. I have read this Patient Information and Informed Consent Form in an understandable language and got answers to all interested questions concerning this study.
2. I have had sufficient time to make a decision.
3. I voluntarily agree to participate in the study described in this Patient Information and Informed Consent Form.
4. I was informed of the names of study team members whom I can contact.
5. I agree that the Sponsor, medical staff of the study and other persons will have access to my medical history as described in this Patient Information and Informed Consent Form.
6. I have got the secondary original of this Patient Information and Informed Consent Form to be kept by me.

Patient's signature

Date (dd/mm/yyyy)

Full name of the patient (please print with your own hand)

Physician-investigator's signature

Date (dd/mm/yyyy)

Full name of the physician-investigator (please print with your own hand)

TABLES

Table 1. Protocol of sample size estimation at frequency comparison for two independent groups, Fisher's exact test, two-sided critical zone (G*Power 3.1.5).

Exact - Proportion: Difference from constant (binomial test, one sample case)

Options:	α balancing: $\alpha/2$ on each side	
Analysis:	A priori: Compute required sample size	
Input:	Tail(s)	= Two
	Effect size g	= 0.1
	α err prob	= 0.05
	Power (1- β err prob)	= 0.8
	Constant proportion	= 0.8
Output:	Lower critical N	= 76
	Upper critical N	= 94
	Total sample size	= 107
	Actual power	= 0.819
	Actual α	= 0.040

Table 2. Protocol of sample size estimation at frequency comparison for two independent groups, Fisher's exact test, two-sided critical zone (G*Power 3.1.5).

Exact - Proportions: Inequality, two independent groups (Fisher's exact test)

Options:	Exact distribution	
Analysis:	A priori: Compute required sample size	
Input:	Tail(s)	= Two
	Proportion p1	= 0.6
	Proportion p2	= 0.9
	α err prob	= 0.05
	Power (1- β err prob)	= 0.8
	Allocation ratio N2/N1	= 5
Output:	Sample size group 1	= 18
	Sample size group 2	= 90
	Total sample size	= 108
	Actual power	= 0.812
	Actual α	= 0.024